IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Confirmation No.: 9371

For: Protein Lattice

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REPLY TO RESTRICTION REQUIREMENT

Commissioner for Patents
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Sir:

Responsive to the Restriction Requirement dated May 13, 2010, Applicants elect, with traverse, *Escherichia coli* (*E. coli*) PurE as a first oligomer assembly, *E. coli* Dps as a second oligomer assembly, and human ferritin heavy chain as a third oligomer assembly. Elected Claims readable on the elected species are Claims 1, 5, 7-25, 35-38, 40 and 42. Applicants reserve the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected inventions. Applicants do not hereby abandon or waive any rights in the non-elected inventions.

The restriction requirement dated May 13, 2010 is being traversed because all of the pending claims share a special technical feature that defines a contribution over the prior art and therefore provides a unity of the invention. One fundamental special technical feature is that Applicants' three-dimensional protein lattices are constructed from at least two protein

protomers, each protein protomer comprising at least a first monomer and a second monomer fused together. Independent Claim 1 recites as follows:

> A protein lattice having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomers, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice (emphasis added).

Grant does not disclose or suggest the use of a protein protomer as defined in the present claims. The Examiner stated that Grant *et al.* (Grant *et al.*, "The Crystal Structure of Dps, a ferritin homolog that binds and protects DNA" *Nature Structural Biology* 5:294-303 (1998); hereinafter, "Grant") teach a crystalline protein lattice comprising *E. coli* Dps protein, which corresponds to all limitations of the claimed protein lattice described in Claim 1. The Examiner stated that "...thus, the shared feature of the group is not a 'special technical feature', unity of invention between the groups does not exist" (Office Action at page 4).

Applicants disagree. The crystal structure described in Grant or any other protein crystal structure constructed by the method described in Grant does not contain a protein protomer of the present invention. Nor does Grant suggest the use of a protein protomer of the present invention. In contrast, as recited in Claim 1 above, the "protein protomer" is an essential element of all protein lattices constructed according to the present invention.

In the present invention, the protein protomer is an essential building block of the protein lattice, which self-assembles into the claimed protein lattice. Each of the protein protomers requires at least two monomers *fused* together. Each of the two monomers is a monomer from an oligomer assembly. The "fusion" as referred to in Claim 1 and used throughout the Specification is a covalent linkage created by an in-frame genetic fusion *via* recombinant technology or

chemical fusion. Such a fusion between two monomers creates a functional protein protomer capable of self-assembly into a protein lattice.

Specifically, in case of a genetic fusion, the Specification teaches that: "The monomers are typically combined to form protomers by fusion of the respective genes at the genetic level (*e.g.*, by removing the stop codon of the 5' gene and allowing an in-frame read through to the 3' gene)" (the Specification at page 19, line 18-24). The protein protomer is then expressed as *a single polypeptide* from the newly combined gene (*see* the Specification at page 19, lines 20-21; emphasis added). In case of a chemical fusion, polypeptides of two monomers are fused post-translationally by means of the *covalent linkage* (*see* the Specification at page 19, lines 25-27; emphasis added). In either case, the protein protomer of the present invention is one continuous entity created by a fusion between two monomers of two oligomer assemblies.

In contrast, the structure described in Grant does not contain any protein protomer of the present invention. Nor does Grant teach or suggest the use of such a protomer. The structure described in Grant is created by packing *E. coli* Dps protein oligomer assemblies in a crystal (*see* Grant, bridging paragraph between 298 and 299). In such a crystal, individual oligomer assemblies come into contact, known as "crystal contact," with each other to establish a protein lattice (*see*, for example, Grant at page 299, left col., first paragraph). Grant's crystallization is typical of the traditional protein crystallization method which depends upon conditions being found under which non-covalent interactions between the groups on the surfaces of protein assemblies occur serendipitously. Grant refers to these interactions as "crystal contacts" between "dodecamers" (*see* Grant at page 298, left col., final paragraph). In the art at the time of the invention, these "crystal contacts" were widely known to be formed only in the process of crystallization and include, for example, polar interactions (*see* Eric Martz, "Protein Crystal Contacts" (2001); "Exhibit A" being submitted herewith). These protein interfaces or interactions do not constitute a permanent bond or covalent linkage as required in a protein protomer ("fusion protein") of the present invention. Thus, unlike the present invention in which individual protein protomers self-assemble into a protein lattice, crystallized *E. coli* Dps protein oligomers described in Grant merely come into contact with each other.

Further, the protein lattices of the present invention are three-dimensional structures as defined in Claim 1. In contrast, the structure described by Grant has repeating units repeating in two-dimensions. Grant expressly states that: "...this packing arrangement resembles multiple

layers of dodecamers in two-dimensional sheets one dodecamer thick" (Grant at page 299, first paragraph; and Fig. 7b).

In sum, the crystal contacts described by Grant are not equivalent to "fusion" of two monomers required in construction of a protein protomer of the present invention. Because the monomers are not fused, the structure described by Grant does not contain a protein protomer which self-assembles into a lattice, an essential feature of the present invention. Accordingly, there exists a special technical feature of Applicants' invention that provides a contribution over the prior art and demonstrates the existence of a unity of invention. Because there is a unity of invention, the Restriction Requirement is improper. Applicants respectfully request that it be withdrawn.

Further, the Examiner stated that "each different combinations of first, second and third oligomer assemblies, which are selected from proteins listed in Claims 35-42, represent a structurally distinct protein lattice with no unity of invention between the group." (Office Action, bridging paragraph between pages 4 and 5). Based on this reasoning, the Examiner required Applicants to elect a single first oligomer assembly from those recited in Claims 35-42; a single second oligomer assembly from those recited in Claims 35-39; and a single third oligomer assembly from those recited in Claims 40-42 (Office Action at page 3).

This requirement is misplaced because Claims 35-42 are not divided into the first, second and third oligomer assemblies. Rather, Claims 35-42 are divided into two main categories: Claims 35-39 are directed to a protein lattice constructed from homologous protomers (a protein lattice having only *a first oligomer assembly and a second oligomer assembly;* for example, *see* Fig. 1); and Claims 40-42 are directed to a protein lattice constructed from heterologous protomers (a protein lattice containing *a first homologous assembly, a heterologous oligomer assembly and a third homologous oligomer assembly*; for example, *see* Fig. 2). Thus, the third homologous oligomer assembly is only relevant to a protein lattice constructed from heterologous protomers.

Claims 35-39 are further divided into three categories based on the order of a rotational symmetry axis, *e.g.*, a protein lattice comprising first and second oligomer assemblies having a rotational symmetry axis of order four (Claims 35 and 36), order three (Claims 37 and 38); and order two (Claims 39). Similarly, Claims 40-42 are also further divided into three categories

based on the order of a rotational symmetry axis of the first and third homologous oligomer assemblies.

The Restriction Requirement is misplaced because Claims 35-42 are not divided by the specific identities of first, second and third oligomer assemblies. Rather, the claims are divided in accordance with the structural features of the oligomer assemblies. For example, electing a single first oligomer assembly from Claim 35 may not be in accordance with the invention if the second oligomer assembly is chosen from Claim 37 because of the difference in the order of the rotational symmetry axes between the two groups.

Because there is a unity of invention and because the Restriction Requirement is based on an improper characterization of the present invention, the Restriction Requirement is fundamentally misplaced. Applicants request that the Restriction Requirement be withdrawn.

An extension of time to respond to the Restriction Requirement is respectfully requested. A Petition for an Extension of Time and the appropriate fee are being filed concurrently.

Respectfully submitted,

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